wherein the htrB mutant endotoxin is the same as wild type endotoxin except for lacking one or more secondary acyl chains of lipid A [lacks one or more secondary acyl chains of lipid A contained in a wild type gram-negative bacterial pathogen and lacks 3-hydroxy unsaturated C16 fatty acid substitutions on the lipid A as compared to a wild-type bacterial pathogen resulting in substantially reduced toxicity when compared to lipid A of the wild type gram-negative bacterial pathogen].

34. (New) The method of claim 22, further comprising the step of purifying the mutant endotoxin.

REMARKS

A. Status of Claims

Reconsideration of this application as amended is requested. Claims 22 and 29 having been amended, claim 34 being newly added, claims 22-26, 29 and 32-34 are pending. No new subject matter has been added.

The amendments to the claims are fully supported by the specification as originally filed. The amendments are made to clarify the claims, and are not intended to limit the scope of equivalents to which any claim element may be entitled. Support for new claim 34 is found in original claim 22. Support for the amendments to claims 22 and 29 is found throughout the specification. One having ordinary skill in the art upon reading the full disclosure would recognize that the claimed mutant endotoxin is the same as wild type endotoxin except for lacking one or more secondary acyl chains of lipid A, i.e., only one change is made between the wild type and mutant endotoxin, and that change is the number of acyl chains in the lipid A. For example, Figure 1 depicts a wild type endotoxin (hexaacyl), and Figures 2A and 2B depict mutant endotoxin (pentaacyl and tetraacyl, respectively). See also Brief Description of the Figures on page 4 of the specification. The only change between Figure 1 and Figures 2A/2B is a decrease in the number of secondary acyl chains. There is no other change in the lipid A (such as length of the remaining chains). Further, page 4, lines 3-9 of the specification states that the lipid A produced by the mutant lacks one or both of the fatty acids, thereby rendering the endotoxin substantially reduced in toxicity, and yet retaining antigenicity as compared to wild

type. Page 7, lines 7-10 states that the mutants specifically lack one or more secondary acyl chain fatty acids that are ester-bound to the hydroxyl grous of two of the four molecules of β-OH. Moreover, on page 13, lines 1-5 of the specification states that the lipid A structure of the mutant endotoxin has one or two fewer acyl chains than the wild type.

It should be noted that "adequate description under the first paragraph of 35 U.S.C. §112 does not require *literal* support for the claimed invention." (emphasis in original) *Ex parte Parks*, 30 USPQ2d 1234-1237, 1236 (Bd. Pat App. 1993); *citing In re Herschler*, 591 F.2d 693, 200 USPQ 711 (CCPA 1979); *In re Edwards*, 568 F.2d 1349, 196 USPQ 465 (CCPA 1978); In re Werthein, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). Rather, it is sufficient if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that an appellant had possession of the concept of what is claimed. *In re Anderson*, 471 F.2d 1237, 176 USPQ 331 (CCPA 1973). As discussed above, clearly one with ordinary skill in the art upon reading the full specification would understand that the claimed mutant endotoxin is the same as wild type endotoxin except for lacking one or more secondary acyl chains of lipid A. Therefore, the claims as currently amended meet the adequate description requirement of 35 U.S.C. §112, first paragraph.

B. Rejections of Claims under 35 U.S.C. §112, First Paragraph

1. Deposit of Microorganisms

Applicant acknowledges that the Examiner has maintained the rejection of claims 22-26 and 29 under 35 U.S.C. § 112, first paragraph and that the rejection will be withdrawn upon the receipt of the required deposit information.

A copy of the deposit receipts and viability statements from the ATCC regarding Nontypeable *Haemophilus influenzae* 2019 B28 and Nontypeable *Haemophilus influenzae* 2019 B29 were submitted along with the Amendment dated December 8, 2000. Also enclosed with the December 8, 2000 Amendment was a Declaration by Dr. Apicella indicating that the strains described in the specification were deposited under the provisions of the Budapest Treaty, and all restrictions will be irrevocably removed upon the granting of a patent on this application, and the deposits will be replaced if viable samples cannot be dispensed by the depository. The Declaration also stated that the strains described in the specification as filed are the same as the

strains deposited in the depository, and the deposited strains were in Applicants' possession at the time of filing of the above-identified application. Therefore, this rejection under 35 U.S.C. § 112, first paragraph should be withdrawn.

2. Written Description

The Examiner has rejected claims 22-26, 29, 32 and 33 as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors at the time the application was filed had possession of the claimed invention. In particular, the Examiner objected to the phrase "lacking 3-hydroxy unsaturated C16 fatty acid substitutions on the lipid A as compared to a wild-type bacterial pathogen". Applicant has now amended the claims to delete this phrase. Therefore, this rejection is rendered moot, and should be withdrawn.

C. Non-Statutory Double Patenting Rejection

The Examiner provisionally rejected the pending claims under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22, 23, 25 and 29 of U.S. Patent Application No. 08/565,943. Applicants will consider filing a terminal disclaimer upon notification of otherwise allowable subject matter. A terminal disclaimer may not be appropriate once the scope of allowable claims is determined in the present application, and dependent upon which application is allowed first.

D. Objection to the Drawings

Corrected formal drawings will be submitted upon notification of allowance of the claims.

E. Distinction of Pending Claims over Previously-Cited Art

1. Karow et al. and Westphal et al.

The pending claims are distinguishable over Karow et al., (*Journal of Bacteriology* 174:7407-7418) in view of Westphal et al. (*Methods Carbonydr. Chem.* 5:83-91, 1965).

The claims as amended recite a method of making a mutant endotoxin, wherein the mutant endotoxin *is the same as* the wild type endotoxin except for lacking one or more secondary acyl chains of lipid A This is clearly distinguishable over Karow et al.

The mutant E. coli identified by Karow et al. makes a set of lipid A structures different from the mutants of the present invention. First, the Karow culture made a fully hexaacylated lipid A structure. §132 Declaration, ¶ 8 (filed on June 30, 2000). The present invention does not include a hexaacylated lipid A structure from *E. coli*. Second, the Karow et al. *E. coli* made an endotoxin containing fewer than six acylated lipid A fatty acids but additionally had changes in the length of the other fatty acid chains. *Id.* For example, the Karow et al. mutant contained a mixture of new unsaturated fatty acids, most likely palmitoleic (C16:1) in place of the single lauric acid (C12:0) fatty acid. *Id.* The lipid A species of the present invention does not contain these changes; the mutant endotoxin of the present invention *is the same as* the wild type endotoxin except for lacking one or more secondary acyl chains of lipid A. Thus, significant differences exist in the lipid A structures in the *htrB* gene deletion mutants of the present invention as compared to Karow's strain. There is simply no teaching in Karow et al. to suggest to those skilled in the art to make a mutation that results in the lipid A recited in the present claims.

Westphal et al. does not remedy the deficiencies of Karow et al. Westphal et al. disclose a method of purifying Gram negative bacterial lipopolysaccharides by phenol-water extraction. They do not, however, teach or suggest a method of making an endotoxin of the present invention, i.e., method of making a mutant endotoxin, wherein the mutant endotoxin *is the same as* the wild type endotoxin except for lacking one or more secondary acyl chains of lipid A

Therefore, the present invention is not obvious over Karow et al. in view of Westphal et al.

2. Karow et al. in view of Westphal et al. and Gupta et al.

The pending claims are distinguishable over Karow et al., (*Journal of Bacteriology* 174:7407-7418) in view of Westphal et al. (*Methods Carbonydr. Chem.* 5:83-91, 1965), and further in view of Gupta et al. (Infect. Immun. 60: 3201-3208, 1992).

Karow et al. and Westphal et al. have been discussed above. Gupta et al. does not remedy the deficiencies of Karow et al. and Westphal et al. Gupta et al. disclose the conjugation of

chemically-modified LPS to cholera toxin and other proteins. They do not, however, teach or suggest a method of making a mutant endotoxin, wherein the mutant endotoxin is the same as the wild type endotoxin except for lacking one or more secondary acyl chains of lipid A.

Therefore, the present invention is not obvious over Karow et al. in view of Westphal et al. and Gupta et al.

CONCLUSION

Applicant believes that all claims are in condition for allowance. Reconsideration of the rejections of the claims and allowance of all the claims is respectfully requested. The Examiner is invited to contact the Applicant's attorney if prosecution of the present application can be assisted thereby.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Box AF, Commissioner of Patents, Washington, D.C. 20231, on this 16th day of March, 2001.

Cindy Brendling
Name

_____
Signature